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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/659,467	09/10/2003	Michael J. Welsh	P05405US01	6078

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EXAMINER	
WEGERT, SANDRA L	
ART UNIT	PAPER NUMBER
1647	
MAIL DATE	DELIVERY MODE
08/20/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/659,467	WELSH ET AL.	
	Examiner	Art Unit	
	SANDRA WEGERT	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 May 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-31* is/are pending in the application.

4a) Of the above claim(s) *5-23 and 26-29* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4, 24, 25, 30 and 31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *10 September 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5/16/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application, Amendments, and/or Claims

The amendment and Information Disclosure Statement, filed 15 May 2008, have been entered and considered. Claims 5-23 and 26-29 are withdrawn. Claim 30 is amended.

Claims 1-4, 24, 25, 30 and 31, (as reading on Post-traumatic Stress Disorder) are under examination.

Withdrawn Objections and/or Rejections

Claim Rejections - 35 USC § 112, second paragraph, indefiniteness.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> **The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter that the applicant regards as his invention.**

The rejection of Claim 30 under 35 U.S.C. 112, -second paragraph, for being indefinite, is *withdrawn*. The rejection was made in the previous Office Action (24 January 2008) because the claim recited a "CNS disorder characterized by extracellular pH." Applicants amended the claim to recite: "CNS disorder characterized by a change in extracellular pH" (15 May 2008), which is more descriptive of the process.

Maintained/New Objections and/or Rejections

Claim Rejections - 35 USC § 112, First Paragraph - Enablement.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> **The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.**

Claims 1-4, 24, 25, 30 and 31 are rejected under 35 USC 112, first paragraph, because the specification does not enable a method of treatment for an anxiety disorder, such as Post-traumatic Stress Disorder (PTSD) *by inhibiting an ASIC channel*. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with the claims.

The claims recite a method of treatment for an anxiety disorder by administering an ASIC ion channel antagonist. Dependent claims list disorders other than PTSD in which anxiety may play a role, several routes of administration, and the requirement that the disorder involve a change in extracellular pH. The specification lays out experiments in which it was shown that ASIC knockout mice show mild deficits in learning a conditioned fear response (see Figure 8), although it was not definitively established if it was generalized anxiety that was lower in these animals, or the ability to learn (or unlearn) a response to novel stimuli. Nonetheless, in vivo experiments were not performed in which ASIC receptors were inhibited or antagonized by adding a drug or antagonist. This is not a trivial matter: No antagonists exist for ASIC receptors. The examiner has not found evidence of general ASIC antagonists or ASIC1 antagonists in the literature, and applicants have not provided any. Applicants performed some

in vitro experiments in which ASIC channels were indeed inhibited, but only by manipulating the pH surrounding the neurons. This technique certainly makes sense, since ASIC receptors are, after all, acid-sensors. However, dropping the pH by 2 points in the culture medium is a crude way to inhibit the cells comprising the channels, and does not translate well to a method of treatment for an anxiety disorder.

The Specification as filed presents data showing the presence of the ASIC receptor in several brain regions involved in conditioning and short-term memory. ASIC receptor knockout mice were produced that had mild deficits in tests of classical conditioning and fear conditioning (Figure 8). The deficits were considered mild based on the fact that they could be overcome with increased training or stronger stimuli (page 34, Specification). Applicants demonstrated deficits in the animals in terms of some cranial nerve reflexes and spatial memory, which is in keeping with the demonstrated locations of ASIC receptors in hippocampus, brainstem and cerebellum (Wemmie, et al, 2002, Neuron, 34: 463-477, of record).

The instant Application does not reasonably provide enablement for a method of treating an anxiety disorder such as PTSD by administering an antagonist of the ASIC receptor. No experiments were performed which measured changes in a disease such as PTSD, which is a uniquely human disease, and considered difficult to treat (Thompson, et al, 2006, BMC Psychiatry, 6(19): 1-10). In the case of claims encompassing medical treatments, additional enabling experiments are needed to confirm that ASIC receptor antagonists can be administered to treat the anxiety disorder. This is critically important since it is not known if all or many anxiety disorders are related to the ASIC receptor.

Applicants discuss the legal requirements for enablement, with which the examiner agrees (Remarks, p.11, 12 May 2008), and cite the case of U.S. v. Telectronics, Inc. (857 F.2d 778, 785, USPQ2d 1217, 1223 (Fed. Cir. 1988)). U.S. v. Telectronics sets forth the amount of further experimentation needed to enable the claimed invention. The application in question in that case involved the use of steel electrodes, the use of which probably did not require as much experimentation as would a method of treatment. Nevertheless, the case has been interpreted to mean that a claimed invention is enabled if any person skilled in the art can make and use the invention without undue experimentation. Such is not the case in the instant application: a method of treatment for PTSD requires further experimentation if no drugs were given in vivo, if humans were not tested, or if an adequate animal model of PTSD was not demonstrated.

Applicants discuss the current state of the art in terms of what is the known relationship between and among acidosis, the amygdala, and conditioned fear (page 12, Remarks, 15 May 2008). Although experimentation is not required for a method of treatment, the art does not disclose a clear nexus between the ASIC receptor and an anxiety disorder, such as PTSD. Although it is difficult to prove a negative, anxiety disorders seem to be under the influence of glutamate and GABA receptors, rather than ASIC receptors (Fenselow & LeDoux, 1999, Neuron, 23: 229-232; Rogan, et al, 1997, Nature 390: 605-608, last paragraph. Both references of record: 9/10/2003). Furthermore, as discussed above, applicants inhibited the ASIC receptor in vitro using very crude non-specific drugs such as amiloride (which non-specifically blocks a sodium channel found in neurons, muscles, skin, lungs, kidneys, and taste receptors). Furthermore, they applied amiloride to the cultured neurons at concentrations that are orders of

magnitude higher than would be useful for in vivo use. A large change in pH would also presumably antagonize these channels (since they are acid-sensing receptors). However, none of these methods has been shown by applicants or by the literature to be effective for in vivo use to treat an anxiety disorder. Applicants have used a crude neuron poison to antagonize hippocampal neurons in vitro, while the literature is silent as to ASIC's role in complex human disorders that we think of as "anxiety disorders."

Furthermore, the specification is not enabling for a method of administering ASIC antagonists orally, topically, sublingually, buccally, intranasally, rectally or intravenously. There was no reduction to practice to support the claims. This is important only because specific ASIC antagonists have not been tested and because it is sometimes difficult to deliver drugs to specific brain areas that might be involved in conditioned fear. Undue experimentation would be required of the skilled artisan to determine the quantity of ASIC antagonist administered, ways to cross the blood-brain-barrier, the best route of administration, any possible side-effects and the duration of treatment needed to successfully treat an anxiety disorder, such as PTSD.

Proper analysis of the Wand's factors was presented in the previous Office Action. Due to the large quantity of experimentation necessary to treat and anxiety disorder such as PTSD using an ASIC receptor antagonist, the lack of direction/guidance presented in the specification regarding same, the absence of working examples directed to same, the complex nature of the invention, and the breadth of the claims--undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

35 USC § 112, first paragraph - Written Description.

Claims 1-4, 24, 25, 30 and 31 are also rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1-4, 24, 25, 30 and 31 are directed to methods of treating an anxiety disorder, such as PTSD, by inhibiting ASIC channels. Dependent claims recite pharmaceutical compositions comprising the ASIC receptor antagonist, as well as several routes of administration of the composition. The Specification as filed describes several experiments that confirm the role of the ASIC1 receptor in conditioning and short-term memory. The Specification also discusses the possible cellular relationship between ASIC channels, pH and GABA-A receptors (Specification, page 2). However, the specification does not teach methods of treating an anxiety disorder in an animal, mammal or human. The description of methods of testing knockout mice behaviorally and of testing cells lacking the ASIC channel, is not adequate written description of a method of treating a uniquely human disease (PTSD), in human patients.

Applicants discuss (Response, 15 May 2008, page 15) the current state of the art in terms of the ASIC channel and antagonists, and point to the use of venoms as possible antagonists of sodium channels. Applicants also refer to a paper by Coryell, et al (Response, 15 May 2008, page 15). The reference was not included in current or previous Information Disclosure Statements, so it could not be determined which publication the citation referred to. Since applicants are making a point that the authors of that publication use a *specific* ASIC antagonist,

it would be useful from the point of Written Description for the examiner to be able to review the reference.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed"* (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed" (See *Vas-Cath* at page 1116).

With the exception of the methods referred to above, the skilled artisan cannot envision the detailed methods needed to treat an anxiety disorder by administering an ASIC antagonist. Conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the methods claimed. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of use. The therapeutic products for the claimed methods are themselves required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016. Applicants have not even disclosed any structural requirements that would be necessary in an ASIC antagonist.

Therefore, only methods of making and behaviorally testing ASIC knockout mice, and methods of antagonizing cultured neurons in vitro, but not the full breadth of the claims, meet the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

References relied upon for a further understanding of the art:

Milad, et al, 2008, J Psychiatr Res. 42(7): 515–520.

Conclusion

Claims 1-4, 24, 25, 30 and 31 are rejected.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Advisory information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sandra Wegert whose telephone number is (571) 272-0895. The examiner can normally be reached Monday - Friday from 9:00 AM to 5:00 PM (Eastern Time). If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Manjunath Rao, can be reached at (571) 272-0939.

The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (in USA or CANADA) or 571-272-1000.

SLW
14 August 2008

/Manjunath N. Rao, /

Supervisory Patent Examiner, Art Unit 1647